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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,275	10/26/2001	Timo Kars van den Berg	080743-235-001	5284

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Ronald A. Sandler
Jones, Day, Reavis & Pogue
77 West Wacker Drive
Chicago, IL 60540

EXAMINER	
YAEN, CHRISTOPHER H	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,275	BERG ET AL.	
	Examiner	Art Unit	
	Christopher H. Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/2/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Berg *et al*
Priority Date: 28 April 2000

1. The amendment filed 12/2/2004 is acknowledged and entered into the record. Accordingly, claims 2-7,9-14 are canceled without prejudice or disclaimer, and claims 15-17 are newly added.

2. Claims 1,8, and 15-17 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, 1st paragraph

4. The rejection of claims 1,8, and now newly added claims 15-17 under 35 USC § 112, 1st paragraph as lacking an enabling disclosure is maintained for the reasons of record. Applicant argues the examiner has not provided sufficient showing that one of skill in the art would engage in undue experimentation to practice the instant invention. Applicant also contends that the examiner provides conclusory statements that the claimed invention is not properly supported. In particular, applicant indicates that the cited reference of Gura does not provide any link to any of the data presented in the instant application, to indicate that there would be undue experimentation to practice the invention or provide any link that the data presented in the application are not reasonable predictive methods for treating an inflammatory disease or treating myeloid leukemia. Applicant also contends that there is no requirement in the US Code, federal regulations or in case law that requires *in vivo* data for enablement. Applicant's

arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

The instant specification provides information with regard to the use of an anti-SIRP antibody or fragments thereof in various in vitro assays (see page 10-11). However aside from this *in vitro* data, the specification has not provided any indication that the claimed method of treating an inflammatory disease or in the treatment of myeloid leukemia could be practice *in vivo* with any reasonable degree of predictability. MPEP 2164.02 indicates that the "[l]ack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." In the instant case, as previously indicated, the treatment of cancer has been deemed unpredictable (see Gura for example) therefore, one of skill in the art would require some indication via working examples or disclosure in the specification that refutes the unpredictable nature of treating cancer. In particular, the working examples of the instant specification tests the affects of an anti-SIRP antibody or fragments thereof on a cultured cell line (i.e. NR8383). The art with respect to the use of in vitro cell has already established that there are differences between cells *in vitro* and *in vivo* (see Freshney and Dermer – previously cited and presented).

In addition, MPEP 2164.03 indicates "[t]he amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or

use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is *unpredictable*, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). In the instant case, it has already been established that the treatment of cancer is at best unpredictable (see Gura), applicant has not provided sufficient disclosure to enable an invention commensurate in scope to the claim because applicant has not provided enough information that the administration of the anti-SIRP compound would be capable of treating *in vivo* as claimed. Such showing can be accomplished by providing working examples commensurate in scope to the claimed invention (i.e. the showing through *in vivo* animal models that the administration of an anti-SIRP antibody or fragment thereof was able to treat cancer or inflammatory disease as claimed OR showing through an in vitro model, that one of skill in the art finds acceptable as indicative or predictive of *in vivo* success, that the administration of anti-SIRP antibody or fragment thereof would in fact treat cancer or inflammatory disease).

With regard to the requirement of *in vivo* data, the issue of correlation is considered. In the instant case, the specification provides in vitro assays of macrophage activity by testing cultured cells lines with an anti-SIRP antibody (see page 10-11). No correlation between these activities *in vitro* have been made to its ability to

function *in vivo*. MPEP 2164.02 states "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition." In the instant case, it has been established that the use of *in vitro* cell assays do not correlate to *in vivo* predictability because of the differences in phenotype and cellular characteristics of *in vitro* cells that have undergone prolonged culturing (see Freshney and Dermer). Thus it has been established in the art that the models presented in the instant specification do not correlate to in vivo effect.

Applicant also directs the examiner's attention to newly submitted figures 1A, 1B, and 2 (Exhibit 2) to indicate that Fab fragments of ED9 effectively inhibits the growth/division of human leukemia cells expressing a chimeric SIRP protein. Applicant concludes that this data indicates that "these *in vitro* assays are reasonably predictive as to whether or not an anti-SIRP substance can inhibit the growth of myeloid leukemia cells, and thus treat myeloid leukemia." Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

Applicant's submission of evidence (exhibit 2) has been carefully considered, however, applicant has not provided any indication or evidence that this new data correlates *in vitro* with *in vivo* capability. Again, the newly submitted figures/data are *in vitro* results and applicant has not provided evidence to indicate that this data is indeed predictable *in vivo*. Applicant only states that the data is reasonably predictive but has

not provided any factual evidence to support such assertions. Essentially, applicant's arguments are opinion not based in fact.

Applicant's additionally argue that the citation of Seiffert *et al* does not mean that those cells that express SIRP would not respond to anti-SIRP. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. The claims in part are drawn broadly to the treatment of all myeloid leukemia. Seiffert *et al* was cited to indicate that the scope of treating all myeloid leukemias is not possible because only AML cells express SIRP. Therefore, the full scope of treating the breadth of myeloid leukemias is unpredictable with regard to treating other forms of leukemia such as CML.

Finally applicant argues that the specification provides sufficient teachings to allow one of skill in the art to successfully practice the invention without undue experimentation. Applicant cites *In re Brana* indicating that "unless there is reason to doubt the objective truth of statements contained [in the specification] which must be relied on for enabling support", a specification 's disclosure must be taken as in compliance with the enabling support." Applicant additionally presents that the Office has the initial burden of presenting evidence that that the skilled artisan would doubt the disclosure. Applicant's also reminds the examiner that the role of the Office is not to determine the safety or effectiveness of a product, and that such determinations are the responsibility of the FDA. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

As indicted above, it has already been established that given the scope of that claimed in the instant invention and the limited disclosure of the specification, one of skill in the art cannot reasonably practice the invention without undue experimentation given the general unpredictability of the art with regard to treating cancer or correlating the *in vitro* with *in vivo* capability. One of skill in the art would therefore doubt that the instant disclosure, which is limited to *in vitro* assays, would be predictable for the treatment of inflammatory disease or in the treatment of cancer. The case has been made because cancer is unpredictable and the correlation between *in vitro* result and in vivo results cannot be made with any reasonable predictability.

In addition, the position of the examiner is not whether the claimed method is safe or effective, but rather has the instant disclosure sufficiently taught one of skill in the art how to use the claimed invention.

Therefore, given the limited disclosure, one of skill in the art cannot practice the invention commensurate in scope to the claims. Thus the rejection of claims under 35 USC 112, 1st paragraph is maintained for the reasons of record.

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 12/2/2004.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
March 10, 2005

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
3/17/05